In accordance with 37 C.F.R. § 1.121, a marked up copy of the presently amended specification paragraphs and claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing. Furthermore, to ensure that Applicants' pending claims match those of the Patent Office, a clean copy of the entire set of pending claims is also appended hereto. No new matter has been added as a result of these amendments.

Claims 1-36 are pending in this application. Claim 34 has been amended. All of the remaining pending claims stand rejected.

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

1. having been altered in any way for any reason related to patentability;

2. having been narrowed;

3. a concession that the invention as patented does not reach as far as the original, unamended claim;

4. a surrender of any subject matter as a condition of receiving a patent; and/or,

5. estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

II. THE RESTRICTION/ELECTION REQUIREMENT

The Examiner states that claim 7 is drawn to a non-elected invention and must be cancelled.

The Applicants ask the Examiner to cancel claim 7 without prejudice. Applicants reserve the right to pursue the subject matter of non-elected claims in this or any appropriate patent application.

The Examiner objects to claims 1-6, 8-29, and 31-36 as containing non-elected subject matter. The Examiner goes on to say:

> The claimed compounds, compositions, and methods that employ them present a variable core. Formula I(b) contains compounds drawn to the non-elected inventions with X other than carbon. Formula I(a) is drawn to non-elected inventions. Office Action p. 2.

In regard to linking claims, the Examiner states that no linking claims have been allowed and the linking claims contain subject matter that was not searched. The Examiner urges the Applicants to amend the claims, so that it need not be done after allowance.

Applicants note that no claims have been allowed and will amend the claims as appropriate when they are allowed.

III. THE 35 U.S.C. § 112, SECOND PARAGRAPH REJECTIONS

A. Claims 1-6, 8-17, 19, 26, 30, and 34-36 remain rejected as indefinite.

The Examiner argues that the term "optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate" is indefinite. The Examiner says:

> While the applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. The term "alicyclic" in claim 1 is used by the claim to mean "alicyclic or saturated heterocyclic," while the accepted meaning is "any aliphatic compound that contains a ring of carbon atoms". The Condensed Chemical Dictionary defines the term as "… carbon atoms in closed ring structures". An alicyclic ring may contain multiple bonds but may not be aromatic and may not contain any heteroatoms. (internal citations omitted)(Office Action pp. 4)

The Examiner suggest removing the reference to non-carbon atoms.

The specification defines the term "alicyclic" as:

> The term "alicyclic" means compounds which combine the properties of aliphatic and cyclic compounds. Such cyclic compounds include but are not limited to, aromatic, cycloalkyl and bridged cycloalkyl compounds. The cyclic compound includes heterocycles. Cyclohexenylethyl and cyclohexylethyl are suitable alicyclic groups. Such groups may be optionally substituted. p. 5

The Examiner cites *In re Hill* from MPEP § 2173.05(a), but neglects to include the rest of the section from the MPEP, which reads:

> However, it has been stated that consistent with the well-established axiom in patent law that a patentee is free to be his or her own lexicographer, a patentee may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings. *Hormone*

Research Foundation, Inc. v. Genentech Inc., 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990).

Numerous Federal Circuit decisions support the concept of the Applicants being their own lexicographers. *See e.g. Jack Guttman Inc. v. Kopykake Enter. Inc.*, 64 U.S.P.Q.2d 1302, 1307 (Fed. Cir. 2002)(saying where, as here, the patentee has clearly defined a claim term, that definition "[u]sually is dispositive; it is the single best guide to the meaning of a disputed term."(quoting *Vitrionics Corp. v. Conceptronic, Inc.*, 39 U.S.P.Q.2d 1573,1577 (Fed. Cir. 1996)); *Trintec Indus. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597, 1599 (Fed. Cir. 2002)(citing *Markman* and saying the inventor may act as his own lexicographer and use the specification to supply implicitly or explicitly new meanings for terms); *CCS Fitness Inc. v. Brunswick Corp.*, 62 U.S.P.Q.2d 1658, 1662 (Fed. Cir. 2002)(stating that the claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term); *Rexnord Corp. v. Laitram Corp.*, 60 U.S.P.Q.2d 1851, 1854 (Fed. Cir. 2001)(stating that patent law permits the patentee to choose to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term that could differ in scope from that which would be afforded by its ordinary meaning); *Hockerson-Halberstadt Inc. v. Avia Group Int'l Inc.*, 55 U.S.P.Q.2d 1487, 1490 (Fed. Cir. 2000)(quoting "it *is always* necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning[because the specification] acts as a dictionary when it expressly defines terms" (*Southwall Techs., Inc. v. Cardinal IG Co.*, 34 U.S.P.Q.2d 1673, 1676 (Fed. Cir. 1995)); *Renishaw plc v. Marposs Societa' per Azioni*, 48 U.S.P.Q. 1117, 1121 (Fed. Cir. 1998)(stating that when an applicant elects to be his own lexicographer by providing an explicit definition, the definition selected by the patentee controls).

The Federal Circuit even reiterated this position in its seminal case on claim construction, *Markman v. Westview Instruments*. In that case, the Federal Circuit said: "As we have often stated, a patentee is free to be his own lexicographer. The caveat is that any special definition given to a word must be clearly defined in the specification." *Markman v. Westview Instruments*, 52 F.3d 967, 980; 34 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 1995)(*en banc*)(internal citations omitted). The Applicants have clearly defined the term "alicyclic" in the specification. Since the Applicants have elected to be their own lexicographers, their definition controls.

As stated in MPEP § 2173, the primary purpose of the requirement for definiteness "is to ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes

infringement of the patent." The Applicants have clearly informed the public of the boundaries of their claims by defining the term "alicyclic" in the specification.

In addition, the term "alicyclic" has been used in various scientific publications to refer to ring structures that contain heteroatoms. In particular, the term "alicyclic amine" is used frequently. The Applicants have enclosed an article from *J. Org. Chem.* showing a secondary alicyclic amine, which is a ring containing a nitrogen.

The Applicants respectfully submit that Claims 1-6, 8-17, 19, 26, 30, and 34-36 are definite and request withdrawal of the rejection.

B. Claims 1-6 and 8-36 remain rejected as indefinite, because the Examiner contends that the phrase "prodrug" is indefinite.

The Examiner states that:

> Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. (Office Action p. 5)

The Examiner goes on to say:

> Applicants correctly point out that their prodrugs are within the scope of claim 1. The Examiner better expresses the concept by noting that their prodrugs are not within the scope of the structural formula given in claim 1. (Office Action p. 5)

The Examiner then explains why he finds the Applicants previous arguments pointing to the "prodrug" definition in the specification unpersuasive:

> Firstly, the passage provides limited structural guidance and defines the phrase in terms of itself. We know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim. Secondly, the passage uses open language "includes but is not limited to". "The groups illustrated are exemplary, not exhaustive". Thirdly, prodrugs of hydroxyl, thiol, and amine containing drugs include 'acyl" esters. Presumably, amine ester means amides since carbonate derivatives of amines are covered by "alkoxycarbonyl". The enablement question for amides is considered separately below. The accepted meaning of "acyl" is "any acid substituent with the OH group removed". Does this include the

> acids of boron and nitrogen? What specific stem, i.e. if acyl is RC(O), what is R? Is it limited to alkanoic acids? Are aromatic, heteroaromatic, alkyl radicals substituted by anything permitted? Are there any limitations? (Office Action p. 6)

The Examiner goes on to explain why he finds the Applicants previous arguments regarding Examples 17 and 18 unpersuasive:

> Example 17 is drawn to the synthesis of compounds of formula (I) where both $R^1Y = NHCHR^{13}CO_2R^{14}$. The Examiner is interpreting "amino acid ester" in line 3 and line 6, page 131 to mean an alkyl ester of a naturally occurring α-amino acid. Example 18 is drawn to compounds of formula (I) where only one of $R^1Y = NHCHR^{13}CO_2R^{14}$. The Examiner has no opinion whether these compounds are, in fact, prodrugs. However, both compounds fall within the scope of formula (I) and fail to clarify which compounds lying outside of the scope of formula (I) are intended. Secondly, assertion is not evidence. In the discussion of the enablement of prodrug. The Examiner cites references showing lack of recognition in the art of medicinal chemistry of what structurally constitutes a prodrug. The Examiner suggest using the language from the passage spanning line 11, page 11 to line 26, page 15, to indicate which prodrugs they intend. (Office Action pp. 6-7).

The Applicants respectfully note that there is nothing wrong with the use of "open language" such as "include but are not limited to" in the specification. The key is whether "the claim apprises one of ordinary skill in the art of its scope." M.P.E.P. § 2173.02. The Applicants assert that a person of ordinary skill in the art can determine what is or what is not a prodrug of the present invention. As Dr. Erion explains in his Declaration, "a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art." (Erion Decl. ¶ 4).

The Applicants note that the term "acyl" is defined in the specification at p. 6 as referring to –C(O)R where R is alkyl or aryl. The term "aryl" is defined in the specification at p. 5, while the term "alkyl" is defined at p. 7. In addition, the term "acyl" is derived from an organic acid not "any acid." (*see e.g.* Hackh's Chemical Dictionary) In view of the specification, a person of ordinary skill in the art would understand what is meant by the term "acyl."

Additionally, the Examiner says he is "interpreting "amino acid ester" in line 3 and line 6, page 131 to mean an alkyl ester of a naturally occurring α-amino acid." (Office Action p. 6) The Applicants respectfully disagree with the Examiner's interpretation, as an amino acid ester can be an ester of any amino acid, not just naturally occurring α-amin acids.

The Applicants respectfully assert that the specification describes the preparation of prodrugs of this invention. (*See* pp. 96-108). Furthermore, prodrug technology is well understood in the art. Dr. Erion explains this further in his declaration saying:

> The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 2000. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

As Dr. Erion has said in his declaration, a person of ordinary skill in the art would have no trouble understanding what is meant by the term "prodrug" as used in the claims of this invention. (Erion Decl. ¶¶ 8 and 10)

Indeed the term "prodrug" is commonly used in patent claims. A recent search of patents issued from 1976 to the present revealed that 343 patents used the term "prodrugs thereof" in the claims. It is clearly a well accepted term in the pharmaceutical industry.

The Examiner continues to object to the use of a functional definition, in spite of case law to the contrary. As stated in MPEP § 2173.05(g), there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

> In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

Furthermore, MPEP § 2173.01 states:

> Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claims which makes clear the boundaries of the subject matter for which the protection is sought. As noted in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

For example, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." *See In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

> In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Furthermore, a "limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable." *In re Fuetterer*, 138 USPQ 217, 222 (C.C.P.A. 1963)(quoting *General Electric Co. v. Wabash Appliance Corp.*, 37 USPQ 466, 469 (U.S. 1938)).

The present situation is similar to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term "inorganic salts" was defined in a functional way. *Id.* at 218-219. The examiner stated that:

> "Inorganic salt" reads on literally thousands of materials, many of which would *not be operative* for applicant's purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

> in the words of the *second* paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of *any* inorganic salt *capable* of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *." It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties.

> We see nothing in the patent law which requires appellant to discover which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no "undue burden" caused by the functional language of the claims:

> The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

Although not directly on point, since the claim in *Fuetterer* was a combination claim, the C.C.P.A. held that the same reasoning applies to elements in claims for compounds. *See In re Barr*, 170 U.S.P.Q. at 336 (stating that although *Fuetterer* was not directly on point "we feel that its rationale, if not its holding, is controlling here.").

As in Fuetterer, it would be an undue burden on the Applicant to list each and every suitable prodrug, as suggested by the Examiner's request to incorporate 4 pages of text from the specification into the claims. The desirability of functional language in these claims is clear.

As stated in *Barr*, the real issue is whether the Applicants have set definite boundaries on the patent protection sought. A person of ordinary skill in the art knows what a prodrug is. A person of ordinary skill in the art would also understand what the boundaries of the invention are, particularly when the claims are viewed in light of the specification. According to MPEP § 2173.02, when "reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claims as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph." Accordingly, there is nothing wrong with defining the term "prodrug" in a functional manner. Nothing requires that the Applicants list each and every suitable prodrug. All that is required is that one of ordinary skill in the art can determine the scope of the claims.

As explained by Dr. Erion in his declaration, a person of ordinary skill in the art can easily determine what is or what is not a prodrug of this invention, such tests are routine, and no undue experimentation is required. (Erion Decl. ¶¶ 4-5, and 10). In addition, Dr. Erion explains that the

preparation of prodrugs is routine. (Erion Decl. ¶ 8). In the telephonic interview, the Examiner indicated that he would give favorable consideration to such a declaration from Dr. Erion. In view of the above arguments and the declaration, the Applicants submit that a person of ordinary skill in the art would not find the use of the term "prodrug" to be indefinite.

Therefore, the Applicants respectfully submit that Claims 1-6, 8-36 are definite and request withdrawal of the rejection.

C. Claim 34 remains rejected as indefinite.

The Examiner believes that the term "a fructose-1,6-bisphosphate dependent disease" is indefinite. The Examiner contends that it is unclear what diseases and treatments are encompassed by the invention. The Examiner goes on to say:

> A claim is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out [sic] such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claim is indefinite. (Office Action pp. 7-8)

In the telephonic interview, the Examiner agreed that the Applicants can claim diabetes, complications of diabetes, and cardiovascular disease. The Applicants respectfully submit that claim 34 is definite as written. However, in order to advance the prosecution of this case, the Applicants have amended claim 34 to recite complications of diabetes and cardiovascular disease.

Therefore, the Applicants believe that claim 34 is definite. The Applicants respectfully request removal of this rejection.

IV. THE 35 U.S.C. § 112, FIRST PARAGRAPH REJECTIONS

A. Claims 1-6 and 8-36 remain rejected as not enabled.

The Examiner believes that determining if a substance is a "prodrug" will require undue experimentation. (Office Action p. 9) The Examiner argues:

> For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, the second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation. (Office Action p. 9)

The Examiner then goes on to say that he found the Applicants' previous arguments unpersuasive. First, the Examiner discusses Wolff (Burger's Medicinal Chemistry) saying:

> [it] states prodrug development requires collaboration between the skilled medicinal chemists and metabolism specialists. All would have a Ph. D. degree and several years of industrial experience...in section 9.1 outlines the research program that must be undertaken to prepare a prodrug. In that paragraph, the difficulties of extrapolating between species in prodrug development are discussed. Thus, the question as to whether a compound is a prodrug in humans will require clinical studies...The working examples to which Applicants point are Examples 17 and 18. The invention concerns chemical synthesis and the pharmacokinetic properties of drug molecules. The state of the art is provided by the references cited by the Applicants and the Examiner. (Office Action pp. 10-11)

The Examiner then goes on to say:

> Applicants use the word prodrug in two different ways. They assert that compounds of formula I are themselves prodrugs and the Applicants claim additional compounds that produce formula (I) upon metabolism. The Examiner has no view whether all, most, some, or any of the compounds of formula (I) are prodrugs. The issue is the compounds whose structures are not defined but lie outside the scope of formula (I). Formulas VI-VIII are embraced by formula (I) and do not provide guidance to the structures of those out that scope. The passage beginning at line 20, page 100 is labeled synthesis of prodrugs but in fact, outlines synthesis of formula (I) and does not provide any guidance to the structures of those out that scope. There are nine types of prodrugs disclosed in the passage spanning line 11, page 11 to line 26, page 15. Most are covered by formula (I) but Formula B, page 11, the right side of Formula E, page 13, Formulas E1,E-2. E3-. and F, page 14, the trichloroethyl ester in the last paragraph on page 15 are outside the scope of formula (I) and constitute guidance in the specification.
>
> Examples 17 and 18, page 130-131, lack any chemical data characterizing the products, and fail to specify the staring [sic] materials used, stating only an "aminoacid ester" is to be used. The two examples give no biological data and do not offer any evidence whether the products of these reactions are or are not prodrugs. Thus, these are prophetic, not working examples. In addition, as discussed above, these do not bear on the question of compounds lying outside the scope of formula (I). In Example I, spanning pages 138-139, Applicants describe a protocol for determining if a compound is a prodrug in rats. There are no results reported and it is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. Thus Applicants have provided no working examples of a prodrug. (Office Action pp. 11-12)

The Examiner goes on to discuss several references. The Examiner says:

> Sanchez (J. Med. Chem.) in the four sentences spanning page 1766 implies that the prodrug nature of an alanate ester was only found empirically after the compound was made. Serafinowska (J. Med. Chem.) in the last complete paragraph on the left side of page 1375 describes the synthesis of thirty-eight potential prodrug phosphonate esters and two amides. Nineteen of these displayed measurable bioavailability. Of these, only seven had bioavailability greater than 10% required of a successful prodrug. It appears that only three of these substances were further evaluated as possible prodrugs. Thus, the skill in the art of synthesis of prodrugs would appear low and not predictable as of 1995.
>
> Bundgaard (J. Med. Chem.) in the second sentence states that a major problem exists in prodrug design, namely designing the proper derivative. The second paragraph makes the point that some ethyl ester prodrugs are hydrolyzed *in vivo* and some are not. Thus, establishing the lack of predictability in the prodrug area as of 1987. Banker (Modern Pharmaceutics) says on page 451, first paragraph that "preparation of prodrugs is becoming a common practice", implying that is not routine as of 1996. Banker (Modern Pharmaceutics) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended and potentially inconclusive research.
>
> Wolff (Medicinal Chemistry) ins second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success of preparing prodrugs. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard protocol discussed in the last sentence of this paragraph is particularly relevant. Finally, concerning the amine containing drugs, Shan (J. Pharmaceutical Sci.) indicates in the first paragraph, page 765 that "[a]pplying similar strategies to the preparation of prodrugs of amine-containing drugs is somewhat more problematic...because of the stability of the amide bond". Thus indicating that the research program outlined above may be inconclusive when applied to drugs that are amines. This also contradicts the paragraph spanning pages 10 and 11 stating that esters of amines (amides) are prodrugs. (Office Action pp. 12-14)

First, the Applicants note that according to the definition in the specification at pp. 10-11 and what is known in the art, "in some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc." Therefore, the first test suggested by the Examiner is not a requirement per se for

prodrugs. However, determining whether a compound meets any of the three criteria set out by the Examiner requires only routine testing.

A person of ordinary skill in the art understands how to make a prodrug and determine if a compound is suitable as a prodrug. A myriad of references describe the routine preparation of prodrugs.

As explained above in Section III.B., MPEP § 2173.05(g) explains that there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

> In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

The key is whether "the claim apprises one of ordinary skill in the art of its scope." M.P.E.P. § 2173.02. As Dr. Erion explains in his Declaration, "a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art." (Erion Decl. ¶ 4). Furthermore, prodrug technology is well understood in the art. Dr. Erion explains this further in his declaration saying:

> The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 2000. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

In fact, the Applicants have provided structural guidance as to what is meant by the term "prodrug." As explained by Dr. Erion

> As defined at p. 10-11 of the specification a prodrug is a compound that undergoes a chemical modification to form a biologically active molecule or a precursor to the biologically active drug. There are many commonly known prodrugs. For example, a compound may have a free hydroxyl group on it. A common prodrug of a hydroxyl is an ester. Esters are often quickly broken down within the body to produce the compound with the free hydroxyl. In this example, the ester is the prodrug. In general, each functional group, *e.g.* hydroxyl, thiol, amine, carboxylic acid, has a set of well described prodrugs that have proven useful for masking the functional group in a manner that enables improved oral bioavailability,

> improved pharmacokinetics, improved distribution, or other properties readily observable during testing in animals and man. (Erion Decl. ¶ 4).

In addition, the specification gives examples for the preparation of prodrugs of this invention. (*See* pp. 96-108). According to MPEP § 2164.01(b), "As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." Dr. Erion explains that "a person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 96-108 of the specification and by the definition of the term "prodrug" at pp. 10-11 of the specification." (Erion Decl. ¶ 8).

There is no requirement that any textbook contain a recipe for making "prodrugs' of the Applicants' invention. The specification describes the preparation of prodrugs of this invention. (*See* pp. 96-108). As Dr. Erion has explained "a person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 96-108 of the specification and by the definition of the term "prodrug" at pp. 10-11 of the specification." (Erion Decl. ¶ 8).

Contrary to the Examiner's position, the prodrug art is not unpredictable. Dr. Erion explains this further in his declaration saying:

> The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 2000. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

As Dr. Erion has said in his declaration, a person of ordinary skill in the art would have no trouble understanding what is meant by the term "prodrug" as used in the claims of this invention. (Erion Decl. ¶¶ 8 and 10).

The Examiner's complaint there are no "working" examples of prodrugs is not a recognized ground in either the MPEP or caselaw for patentability of claims. The Examiner admitted that the specification contains paper examples for prodrug activity. The MPEP and caselaw recognize the adequacy of paper examples to support claims. MPEP § 2164.02 ("Compliance with the enablement

requirement of 35 U.S.C. 112, first paragraph, does not turn on whether a working example is disclosed."); *Gould v. Quigg*, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." citation omitted).

The Examiner cites several references to show that the prodrug art is not predictable. (Office Action pp. 12-14) The Applicants do not believe that this is the proper interpretation of these references. As explained by Dr. Erion in his declaration, a person of ordinary skill in the art can easily determine what is or what is not a prodrug, such tests are routine, and no undue experimentation is required. (Erion Decl. ¶¶ 4-5, and 9-10). The fact that some testing is required does not mean that the prodrug art is "unpredictable." The Examiner also cites Serafinowska and Bundgard to show that the prodrug art was not predictable in 1996 or 1987. (Office Action pp. 12-13) The Applicants note that neither 1996 nor 1987 is the filing date of this Application. State of the art in 1996 or 1987 is not necessarily state of the art in 2000.

The Examiner refers to *Banker* and interprets the phrase "preparation of prodrugs is becoming a common practice" to mean that it is not routine of 1996. (Office Action p. 14). As above, the Applicants are not clear that this is the proper interpretation of the phrase from *Banker*. In fact, this phrase would indicate the opposite, that the preparation of prodrugs is standard in 1996. Even if prodrug preparation was not standard in 1996, 1996 is not the filing date of this Application. State of the art in 1996 is not necessarily state of the art in 2000, particularly when it comes to textbooks that are written well in advance of publication.

The Examiner also points to the research program outlined in *Wolff* and to the phrase "extensive development must be undertaken to find the correct chemical modification" in *Banker* as "an invitation to open-ended and potentially inconclusive research." (Office Action p. 14). Again, the Applicants respectfully disagree with the Examiner's interpretation of these textbook sections. The Examiner appears to take these quotations out of context. For instance, the standard for getting a drug approved for use in humans by the FDA is a completely different standard from that required for patentability.

In any event, the Applicants are not clear as to why the Examiner finds these textbooks persuasive. The enablement requirement does not require that there be no experimentation. As stated in M.P.E.P. § 2164.01:

> The fact that some experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation...The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, it is undue. M.P.E.P. § 2164.01 (internal citations omitted)

In fact, Dr. Erion has explained that a person of ordinary skill in the art can routinely prepare the prodrugs of this invention without undue experimentation. (Erion Decl. ¶ 8) It should be noted that the Court has cautioned against the Examiner substituting his opinion for that of one skilled in the art. For example when speaking to an obviousness rejection, the Court said:

> We do not think it was the intent of section 103 that either the examiner, the board, or this court should substitute their own speculations for the factual knowledge of those skilled in the art. Where, as here, an affidavit states facts which are relevant to the ultimate determination of the legal issue arising under 103, we think it must be given careful evaluation and properly weighed to determine whether it factually rebuts the bases upon which the examiner has predicated his findings of obviousness. *In re Katzschmann*, 146 U.S.P.Q. 66, 68 (C.C.P.A. 1965).

Finally, the Applicants did not mean to imply that prodrug technology was routine in the late nineteenth century, but merely that prodrugs have been in use for a long time.

As explained by Dr. Erion in his declaration, a person of ordinary skill in the art can easily determine what is or what is not a prodrug of this invention, such tests are routine, and no undue experimentation is required. (Erion Decl. ¶¶ 4-5, and 9). In addition, Dr. Erion explains that the preparation of prodrugs is routine. (Erion Decl. ¶ 8). In the telephonic interview, the Examiner indicated that he would give favorable consideration to such a declaration from Dr. Erion. In view of the above arguments and the declaration, the Applicants submit that a person of ordinary skill in the art would find that the claims are enabled.

The Applicants submit that they have thus satisfied the enablement requirement. Therefore, the Applicants respectfully request withdrawal of the rejection that Claims 1-6 and 8-36 are not enabled.

B. Claim 34 remains rejected as not enabled.

The Examiner contends that while the specification is enabling for treatment of diabetes, it is not enabling for treatment of "a fructose-1,6-biphosphatase dependent disease" generally. The Examiner states:

> Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as diabeteis [sic] pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy. (Office Action p. 14).

In the telephonic interview, the Examiner agreed that the Applicants can claim diabetes, complications of diabetes, and cardiovascular disease. The Applicants respectfully submit that claim 34 is enabled as written. However, in order to advance the prosecution of this case, the Applicants have amended claim 34 to recite complications of diabetes and cardiovascular disease.

In view of the above, Applicants respectfully request removal of the rejection that claim 34 is not enabled.

C. Claims 36 remains rejected as not enabled.

The Examiner contends that while the specification is enabling for treatment of diabetes, it is not enabling for treatment of "glycogen storage diseases" generally. The Examiner states:

> Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as diabeteis [sic] pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy. (Office Action p. 15-16).

The Examiner goes on to say:

> Applicants have clarified that these diseases are the enzyme deficiency disorders of seven specific types of glycogenosis as (Cori classification) and as further described in Chen (Principles of Internal Medicine). The Table 347-1 on page 2178 of Chen (Principles of Internal Medicine) teaches that none of these diseases involves fructose-1,6-bisphosphaaste [sic]. The only glycogen storage disease involving fructose is type VII, Tarui disease. This disease is caused by a deficiency of the phosphofructokinase enzyme. The Figure 347-1 on page 2177 makes clear that this is a different enzyme than fructose-1,6-bisphosphaaste [sic]. Why do Applicants believe that their fructose-1,6- bisphosphaaste [sic] will be benefication for any of these enzyme disorders? (Office Action p. 16)

During the telephonic interview, the Examiner agreed with the Applicants explanation that anything that inhibits glucose would be helpful in inhibiting the build-up of glycogen. Since FBPase inhibitors inhibit glucose, they are helpful in inhibiting the build-up of glycogen, and thus useful in treating glycogen storage diseases. Therefore, claim 36 is enabled. Applicants respectfully request removal of the rejection that claim 36 is not enabled.

D. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 stand rejected as lacking written description.

The Examiner says:

> The two provisos in the next to last three lines of claim 1 lack written description. Nowhere in the specification is such a relationship linking the description among radical R^5 and radicals J^2-J^6 described. Such a negative limitation requires description. In *Ex parte Grasselli*, et al. 231 USPQ393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts." (Office Action pp. 16-17)

As stated in the MPEP § 2163, in order to "satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." In *In re Wertheim*, the Court said "[i]t is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosures that appellants invented processes for including those limitations." *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)(internal citations omitted). In *Wertheim*, the disputed term was the limitation "between 35% and 60%." *Id.* at 98. The specification recited a broader range of 25-60%. The Court found that the narrower limitation had adequate written description saying "we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of the appellants' invention." *Id.* The Court went on to say "[i]f lack of literal support alone were enough to support a rejection under § 112, then the statement of *In re Lukach*, that 'the invention

claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of § 112,' is empty verbiage." *Id.* (internal citations omitted).

In a more analogous case, the applicants faced a 102 rejection unless they could claim the benefit of an earlier filed application. *In re Driscoll*, 195 U.S.P.Q. 434, 436 (C.C.P.A. 1977). The priority application had a Markush group wherein R was selected from the group consisting of 14 groups. *Id.* at 436. The claim in the application at issue allowed R to be only one of those 14 groups. *Id.* at 435. The Examiner and Board found that the applicants were not entitled to the earlier filing date, since they believed that the earlier application lacked an adequate written description for the new claim. *Id.* at 436.

The Court disagreed saying:

> We thus agree with appellant that a skilled artisan would recognize from the disclosure of S.N.782,756 fourteen distinct classes of compounds, each class having a single member of the R group at the 5-position of the thiadiazole moiety and variable substituent groups on the urea moiety. This being the case, it follows that S.N.782,756 describes the subject matter of claim 13 inasmuch as one of the fourteen classes of compounds is the 5-alkylsulfonyl-1,3,4-thiadiazole ureas defined therein. *Id.* at 437-38.

The Court went on to criticize the decision by the Examiner and the Board as "a hypercritical application" of the written description requirement. *Id.* at 438. The Court felt that upholding the Board's decision would create a predicament for future applicants where:

> If, when [applicants] yield any part of what they originally believed to be their due, they substitute a new "invention," only two courses will be open to them: they must at the outset either prophetically divine what the art contains, or they must lay down a barrage of claims, starting with the widest and proceeding by the successive incorporation of more and more detail, until all combinations have been exhausted which can by any possibility succeed. The first is an impossible task; the second is a custom already more honored in the breach than in the observance, and its extension would only increase that surfeit of verbiage which has for long been the curse of patent practice, and has done much to discredit it. It is impossible to imagine any public purpose which it could serve. *Id.* (internal citation omitted)

Such is the case here, adding a proviso that yields part of what was the originally claimed invention should not constitute new matter.

The *Ex Parte Grasselli* case cited by the Examiner is distinguished in that it appears that the specification in that case did not disclose a Markush group of possible catalysts and then only claim

some of the catalysts in the later application. *Ex Pare Grasselli,* 231 U.S.P.Q. 393, 394 (Bd. Pat. App. & Int. 1983). Based on the sketchy facts of the case, it appears that the applicants added provisos eliminating certain catalysts found in the prior art, when they had not named possible catalysts before. *Id.* This Application is distinguishable in that the specification and claim 1 have disclosed Markush groups for R^5 and L. The proviso merely yields part of what was originally claimed. The proviso has not added new matter.

A person of skill in the art would understand that the Applicants had possession of the invention claimed in claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29. The provisos do not constitute new matter and do satisfy the written description requirement. Therefore, Applicants respectfully request the removal of this rejection.

V. THE 35 U.S.C. § 102 REJECTION

Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 remain rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,640,701 ("the '701 patent"). The Examiner contends that two of the compounds taught by the '701 patent fit formula I compounds of the above claims. The Examiner admits that the provisos overcome the rejection, but finds that the provisos are new matter.

As explained above, the provisos do not constitute new matter and do satisfy the written description requirement. Therefore, Applicants respectfully request the removal of this rejection.

Conclusion

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully Submitted,

Date: 5/27/03

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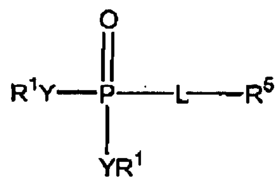
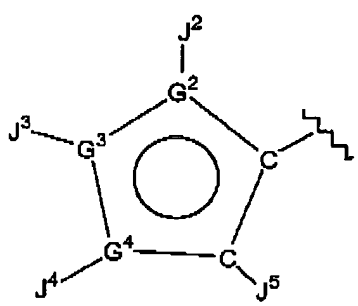
Marked Up Version of the Claims

34. (Once Amended) A method of treating [a fructose-1,6-bisphosphatase dependent disease or condition] complications of diabetes or cardiovascular diseases in an animal which comprises administering to an animal suffering from [a fructose-1,6-bisphosphatase dependent disease or condition] complications of diabetes or cardiovascular diseases a pharmaceutically effective amount of a compound of formula (I):



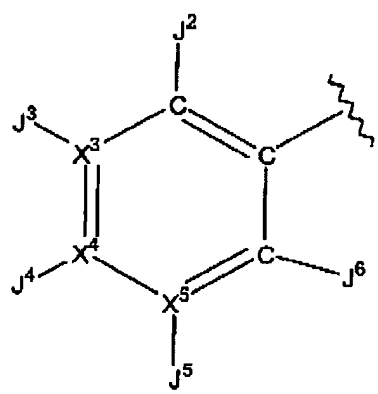
(I)

wherein R^5 is selected from the group consisting of:



I (a)

and



I (b)

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4{}_2$, $-CONR^4{}_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4{}_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-$NR^4{}_2$, -alkylene-CN, -CN, $-C(S)NR^4{}_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4{}_2$, and $-NR^{18}COR^2$;

L is selected from the group consisting of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

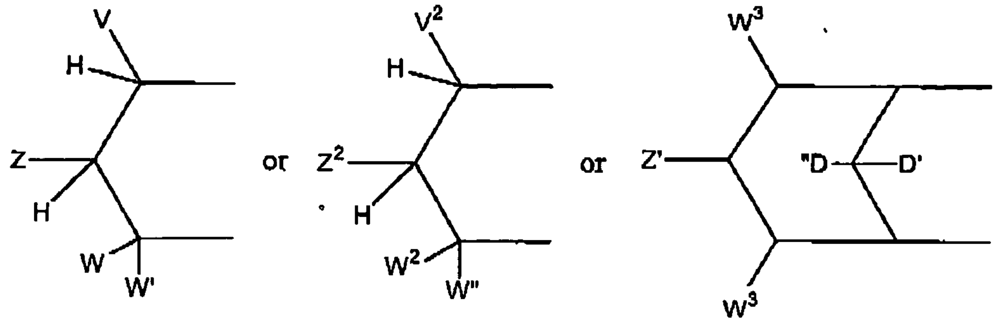
ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, -alkylenethio-, -alkylenecarbonyloxy-, -alkylene-S(O)-, -alkylene-$S(O)_2$-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkylene-S-$C(O)R^3$, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is $-NR^6-$, and R^1 attached to it is $-(CR^{12}R^{13})_n-C(O)-R^{14}$, then the other YR^1 is selected from the group consisting of $-NR^{15}R^{16}$, $-OR^7$, and $NR^6-(CR^{12}R^{13})_n-C(O)-R^{14}$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2$NHaryl, $-CH_2$aryl; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy,

alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and –C(O)-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when G^2, G^3, or G^4 is O or S, then the respective J^2, J^3, or J^4 is null;

3) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

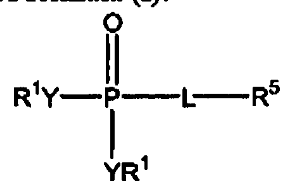
4) if both Y groups are $-NR^6$-, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n$-C(O)-R^{14};

5) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6$-$C(R^{12}R^{13})_n$-C(O)-R^{14};

and pharmaceutically acceptable prodrugs and salts thereof.

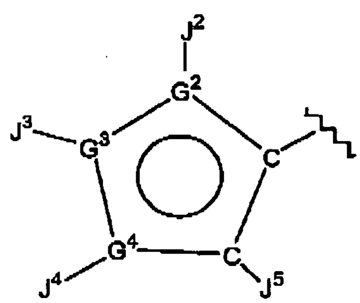
PENDING CLAIMS

1. (Oncc Amended) A compound of formula (I):

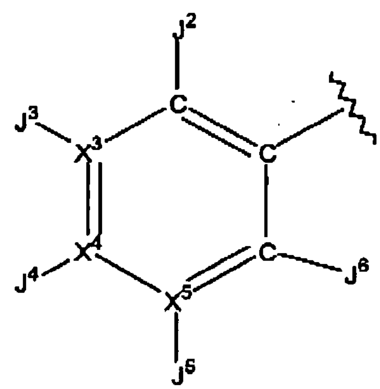


(I)

wherein R^5 is selected from the group consisting of:



and



I (a) I (b)

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$,

-alkylene-NR^4_2, -alkylene-CN, -CN, -C(S)NR^4_2, -OR^2, -SR^2, -N_3, -NO_2, -NHC(S)NR^4_2, and –$NR^{18}COR^2$;

L is selected from the group consisting of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

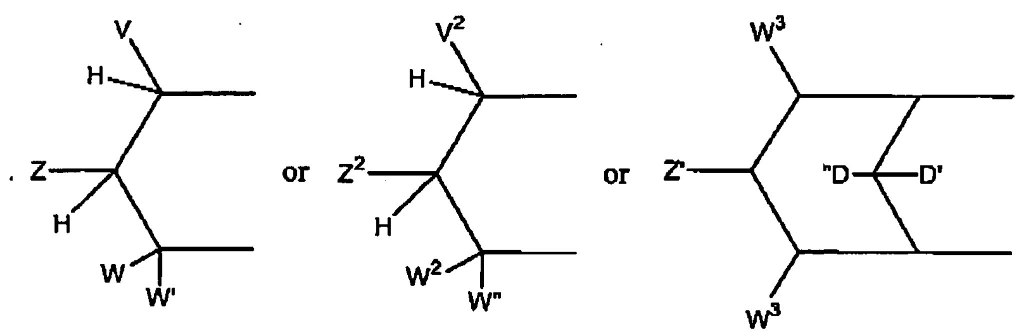
ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkylene-S-C(O)R^3, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is –NR^6-, and R^1 attached to it is –$(CR^{12}R^{13})_n$-C(O)-R^{14}, then the other YR^1 is selected from the group consisting of –$NR^{15}R^{16}$, -OR^7, and NR^6-$(CR^{12}R^{13})_n$-C(O)-R^{14};

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NH$aryl, $-CH_2$aryl; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and –C(O)-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when L is substituted furanyl, then at least one of J^2, J^3, J^4, and J^5 is not –H or null;

3) when L is not substituted furanyl, then at least two of J^2, J^3, J^4, and J^5 on formula I(a) or J^2, J^3, J^4, J^5, and J^6 on formula I(b) are not –H or null;

4) when G^2, G^3, or G^4 is O or S, then the respective J^2, J^3, or J^4 is null;

5) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

6) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

7) when L is –alkylenecarbonylamino- or -alkyleneaminocarbonyl-, then X^3, X^4, and X^5 are not all C;

8) when L is –alkeneoxyalkylene-, and X^3, X^4, and X^5 are all C, then neither J^3 nor J^5 can be substituted with an acylated amine;

9) when R^5 is substituted phenyl, then J^3, J^4, and J^5 is not purinyl, purinylalkylene, deaza-purinyl, or deazapurinylalkylene;

10) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$;

11) when R^5 is substituted phenyl and L is 1,2-ethynyl, then J^3 or J^5 is not a heterocyclic group;

12) when L is 1,2-ethynyl, then X^3 or X^5 cannot be N;

and pharmaceutically acceptable prodrugs and salts thereof;

13) when R^5 is substituted phenyl and L is –alkyleneoxycarbonyl-, then J^3 or J^5 is not O-aryl;

14) when R^5 is substituted phenyl and L is 1,2-ethynyl, then at least one of J^2, J^3, J^4, J^5, and J^6 is not H or null.

2. The compounds of claim 1 wherein R^5 is selected from the group consisting of substituted phenyl, substituted pyrrolyl, substituted oxazolyl, substituted thiazolyl, substituted isothiazolyl, substituted pyrazolyl, substituted isoxazolyl, substituted pyridinyl, substituted thienyl, substituted furanyl, substituted pyrimidinyl, and substituted pyridazinyl.

3. The compounds of claim 1 with the further proviso that when L is -alkyleneoxyalkylene-, and R^5 is substituted thienyl, substituted furanyl, or substituted phenyl, then J^3, J^4, or J^5 is not halo or alkenyl.

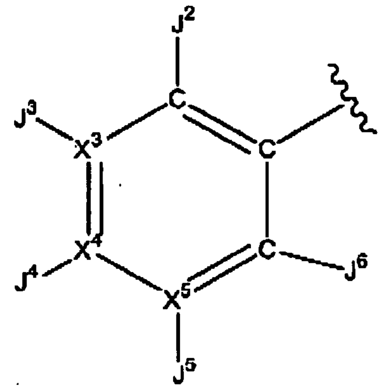
4. The compounds of claim 1 with the further proviso that when L is -alkyleneoxyalkylene-, then R^5 is not substituted thienyl, substituted furanyl, or substituted phenyl.

5. The compounds of claim 1 with the further proviso that when L is -alkyleneoxycarbonyl-, and X^3, X^4, and X^5 are all C, then neither J^2 nor J^6 is a group attached through a nitrogen atom.

6. The compounds of claim 1 with the further proviso that when L is –alkyleneoxyalkylene- or –alkyleneoxycarbonyl-, then R^5 is not substituted phenyl.

7. (Removed from consideration by Examiner)

8. The compounds of claim 1 wherein R^5 is a compound of formula I(b):



I (b)

9. The compounds of claim 1 wherein L is selected from the group consisting of:

i) 2,5-furanyl, 2,5-thienyl, 2,6-pyridyl, 2,5-oxazolyl, 5,2-oxazolyl, 2,4-oxazolyl, 4,2-oxazolyl, 2,4-imidazolyl, 2,6-pyrimidinyl, 2,6-pyrazinyl, 1,3-phenyl;

ii) 1,2-ethynyl; and

iii) a linking group having 3 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of -alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, and -alkyleneoxyalkylene-.

10. The compounds of claim 9 wherein L is selected from the group consisting of:

i) 2,5-furanyl, 2,5-thienyl, 2,6-pyridyl, 2,5-oxazolyl, 5,2-oxazolyl, 2,4-oxazolyl, 4,2-oxazolyl, 2,4-imidazolyl, 2,6-pyrimidinyl, 2,6-pyrazinyl, 1,3-phenyl; and

ii) 1,2-ethynyl.

11. The compounds of claim 9 wherein L is selected from the group consisting of:

i) 2,5-furanyl, 2,6-pyridyl, 2,5-oxazolyl, 2,4-imidazolyl, 1,3-phenyl;

ii) 1,2-ethynyl; and

iii) a linking group having 3 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of -methylenecarbonylamino-, -methyleneaminocarbonyl-, -methyleneoxycarbonyl-, and -methyleneoxymethylene-.

12. The compounds of claim 11 wherein L is selected from the group consisting of 2,5-furanyl, methyleneoxycarbonyl, methyleneoxymethylene, and methyleneaminocarbonyl.

13. The compounds of claim 12 wherein L is 2,5-furanyl.

14. The compounds of claim 1 wherein X^4 and X^5 are C.

15. The compounds of claim 1 wherein J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of –H, $-NR^4_2$, $-C(O)NR^4_2$, $-CO_2R^3$, halo, $-SO_2NR^4_2$, lower alkyl, lower alkenyl, lower alkynyl, lower perhaloalkyl, lower haloalkyl, lower aryl, lower alkylaryl, lower alkylene-OH, $-OR^{11}$, $-CR^2_2NR^4_2$, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, $-NR^{18}C(O)R^2$ and $-CR^2_2CN$.

16. The compounds of claim 12 wherein J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of –H, $-NO_2$, lower alkyl, lower alkylaryl, lower alkoxy, lower perhaloalkyl, halo, $-CH_2NHR^4$, $-C(O)NR^4_2$, $-S(O)_2NHR^4$, -OH, $-NH_2$, and $-NHC(O)R^2$.

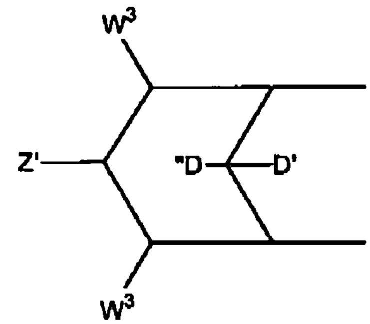
17. The compounds of claim 1, where both Y groups are -O-.

18. The compounds of claim 1, where both Y groups are $-NR^6-$.

19. The compounds of claim 1 where one Y is $-NR^6-$, and one Y is –O-.

20. The compounds of claim 1 wherein each YR^1 is –OH.

21. The compounds of claim 1 wherein R^1 and R^1 together are



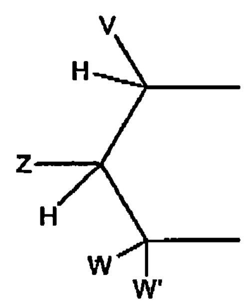
Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$; and

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl.

22. The compounds of claim 1 wherein R^1 and R^1 together are



V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

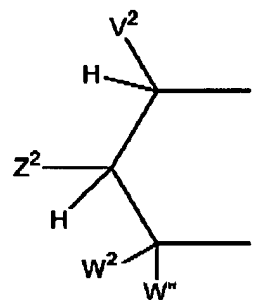
together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

23. The compounds of claim 1 wherein R^1 and R^1 together are



V^2, W^2 and W'' are independently selected from the group of –H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NH$aryl, $-CH_2$aryl; or

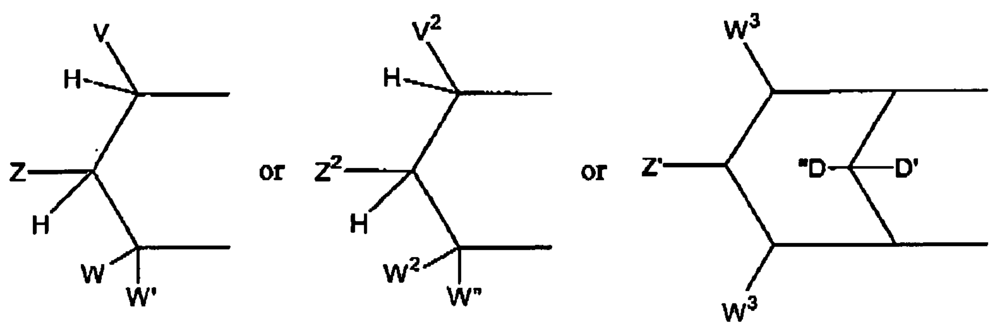
together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus.

24. The compounds of claim 1 wherein when both Y groups are -O-, then R^1 attached to -O- is optionally substituted aryl.

25. The compounds of claim 1 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of optionally substituted aralkyl.

26. The compounds of claim 1 wherein both Y groups are -O-, and at least one R^1 is selected from the group consisting of $-C(R^2)_2-OC(O)R^3$, and $-C(R^2)_2-OC(O)OR^3$.

27. The compounds of claim 1 wherein at least one Y is -O-, and together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D'' is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

b) both Y groups are not $-NR^6-$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl.

28. The compounds of claim 1 wherein one Y is -O-, and R^1 is optionally substituted aryl; and the other Y is $-NR^6-$, where R^1 attached to said $-NR^6-$ is selected from the group consisting of $-C(R^4)_2C(O)OR^3$, and $-C(R^2)_2C(O)OR^3$.

29. The compounds of claim 1 wherein

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of –H, $-NR^4{}_2$, $-CONR^4{}_2$, $-CO_2R^3$, halo, $-SO_2NR^4{}_2$, lower alkyl, lower alkenyl, lower alkylenearyl, lower alkynyl, lower perhaloalkyl, lower haloalkyl, lower aryl, lower alkylene-OH, $-OR^{11}$, $-CR^2{}_2NR^4{}_2$, -CN, $-C(S)NR^4{}_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4{}_2$, $-NR^{18}COR^2$, $-CR^2{}_2CN$;

L is selected from the group consisting of

i) 2,5-furanyl, 2,5-thienyl, 1,3-phenyl, 2,6-pyridyl, 2,5-oxazolyl, 5,2-oxazolyl, 2,4-oxazolyl, 4,2-oxazolyl, 2,4-imidazolyl, 2,6-pyrimidinyl, 2,6-pyrazinyl;

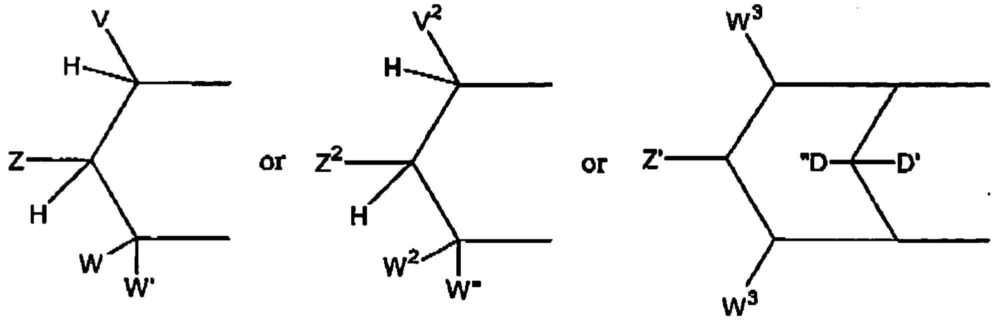
ii) 1,2-ethynyl; and

iii) a linking group having 3 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, and -alkyleneoxyalkylene-;

when both Y groups are -O-, then R^1 is independently selected from the group consisting of optionally substituted aryl, optionally substituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H; or

when one Y is -O-, then R^1 attached to -O- is optionally substituted aryl; and the other Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is selected from the group consisting of $-C(R^4)_2C(O)OR^3$, and $-C(R^2)_2C(O)OR^3$; or

when Y is -O- or $-NR^6-$, then together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2$NHaryl, $-CH_2$aryl; r

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and alicyclic; and

b) both Y groups are not $-NR^6-$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl.

30. (Amended) The compounds of claim 2 wherein R^5 is substituted phenyl;

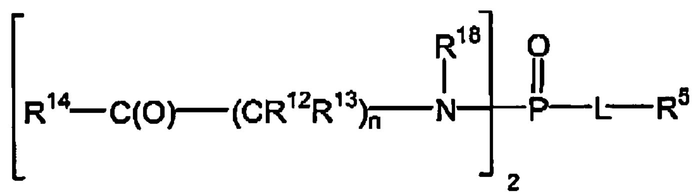
L is furan-2,5-diyl; J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of $-OR^3$, $-SO_2NHR^4$, -CN, –H, halo, $-NR^4_2$, $-(CH_2)_2$aryl, $-(CH_2)$NHaryl, and $-NO_2$; at least one Y group is -O-.

31. The compounds of claim 1 wherein

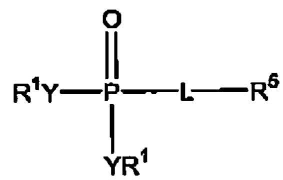
one Y is $-NR^6-$, and R^1 attached to it is $-(CR^{12}R^{13})_n-C(O)-R^{14}$, then the other YR^1 is selected from the group consisting of $-NR^{15}R^{16}$, $-OR^7$, and $NR^6-(CR^{12}R^{13})_n-C(O)-R^{14}$.

32. The compounds of claim 31 wherein the other YR^1 is $-OR^7$.

33. The compounds of claim 1 that are of the formula:

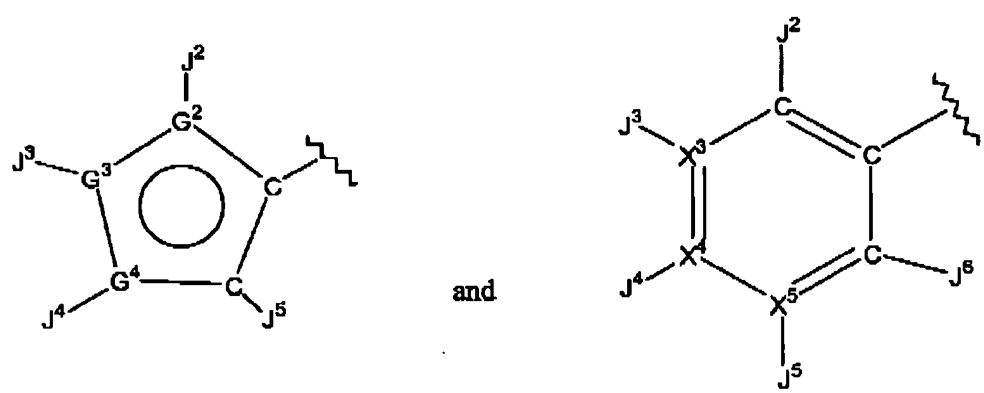


34. (Once Amended) A method of treating complications of diabetes or cardiovascular diseases in an animal which comprises administering to an animal suffering from complications of diabetes or cardiovascular diseases a pharmaceutically effective amount of a compound of formula (I):



(I)

wherein R^5 is selected from the group consisting of:



I (a) and I (b)

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-NR^4_2, -alkylene-CN, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{18}COR^2$;

L is selected from the group consisting of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

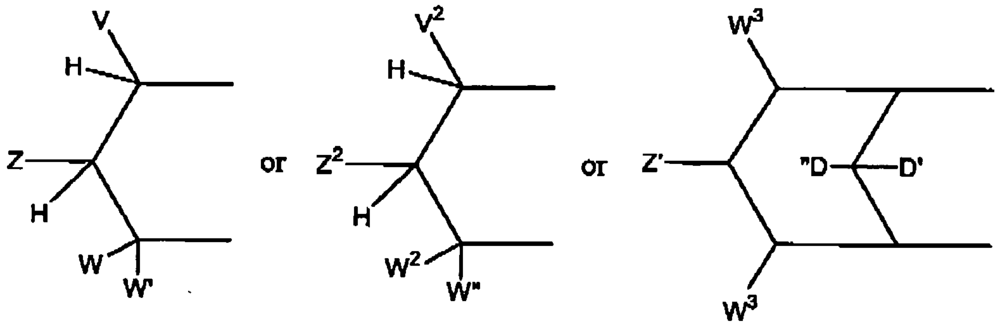
ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, -alkylenethio-, -alkylenecarbonyloxy-, -alkylene-S(O)-, -alkylene-$S(O)_2$-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkylene-S-$C(O)R^3$, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is $-NR^6-$, and R^1 attached to it is $-(CR^{12}R^{13})_n-C(O)-R^{14}$, then the other YR^1 is selected from the group consisting of $-NR^{15}R^{16}$, $-OR^7$, and $NR^6-(CR^{12}R^{13})_n-C(O)-R^{14}$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, r together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a

chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and $-C(O)$-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when G^2, G^3, or G^4 is O or S, then the respective J^2, J^3, or J^4 is null;

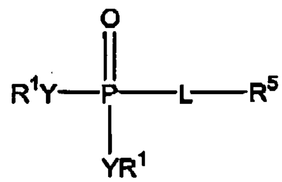
3) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

4) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

5) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$;

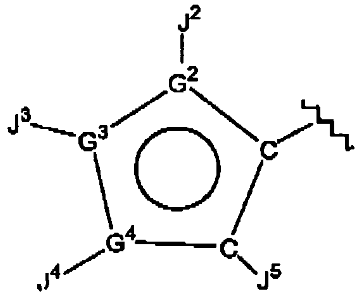
and pharmaceutically acceptable prodrugs and salts thereof.

35. A method of treating diabetes, by administering to patient in need thereof a pharmaceutically effective amount of an FBPase inhibitor of Formula I:



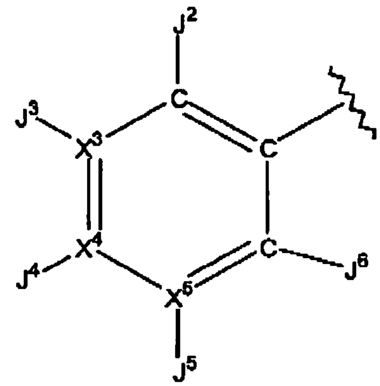
(I)

wherein R^5 is selected from the group consisting of:



I (a)

and



I (b)

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-NR^4_2, -alkylene-CN, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{18}COR^2$;

L is selected from the group consisting of:

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i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

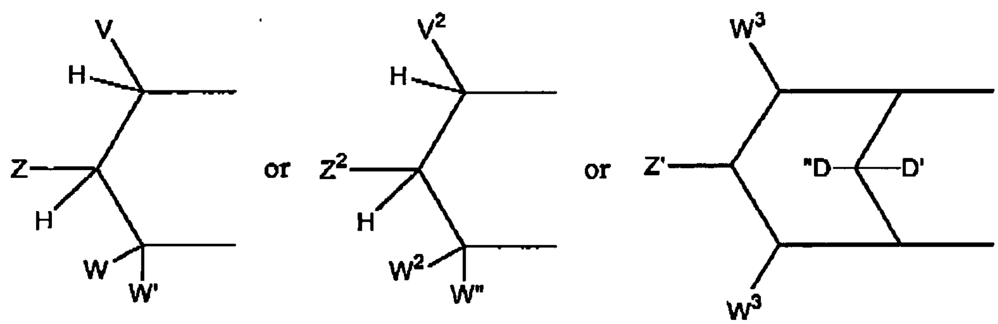
ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, -alkylenethio-, -alkylenecarbonyloxy-, -alkylene-S(O)-, -alkylene-$S(O)_2$-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, -$C(R^2)_2OC(O)NR^2{}_2$, -NR^2-$C(O)$-R^3, -$C(R^2)_2$-$OC(O)R^3$, -$C(R^2)_2$-O-$C(O)OR^3$, -$C(R^2)_2OC(O)SR^3$, -alkylene-S-$C(O)R^3$, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is –NR^6-, and R^1 attached to it is –$(CR^{12}R^{13})_n$-$C(O)$-R^{14}, then the other YR^1 is selected from the group consisting of –$NR^{15}R^{16}$, -OR^7, and NR^6-$(CR^{12}R^{13})_n$-$C(O)$-R^{14};

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2$NHaryl, $-CH_2$aryl; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D'' is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and –C(O)-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when G^2, G^3, or G^4 is O or S, then the respective J^2, J^3, or J^4 is null;

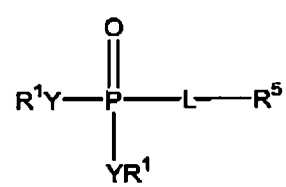
3) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

4) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

5) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$;

and pharmaceutically acceptable prodrugs and salts thereof.

36. A method of treating glycogen storage diseases, by administering to a patient in need thereof a pharmaceutically effective amount of an FBPase inhibitor of formula I:



(I)

wherein R^5 is selected from the group consisting of:

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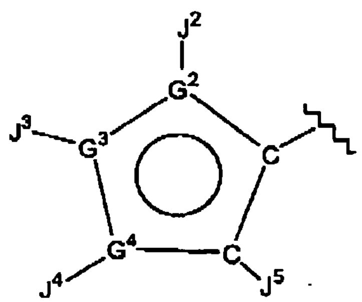
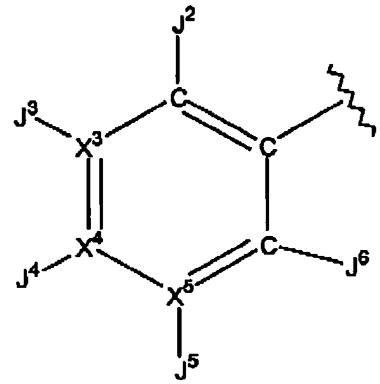


I (a)

and



I (b)

wherein:

G^2 is selected from the group consisting of C, O, and S;

G^3 and G^4 are independently selected from the group consisting of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 may be O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

X^3, X^4, and X^5 are independently selected from the group consisting of C and N, wherein no more than two of X^3, X^4, and X^5 may be N;

J^2, J^3, J^4, J^5, and J^6 are independently selected from the group consisting of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-NR^4_2, -alkylene-CN, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{18}COR^2$;

L is selected from the group consisting of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group consisting of –alkylenecarbonylamino-, -alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-,

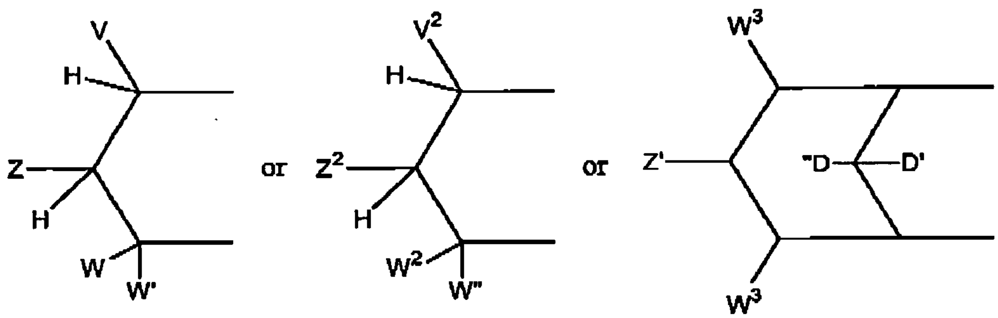
-alkyleneoxy-, -alkylenethi -, -alkylenecarbonyloxy-, -alkylene-S(O)-, -alkylene-S(O)$_2$-, and –alkyleneoxyalkylene-, all of which may be optionally substituted;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, -C(R^2)$_2$OC(O)NR^2$_2$, -NR^2-C(O)-R^3, -C(R^2)$_2$-OC(O)R^3, -C(R^2)$_2$-O-C(O)OR^3, -C(R^2)$_2$OC(O)SR^3, -alkylene-S-C(O)R^3, -alkylene-S-S-alkylenehydroxy, and -alkylene-S-S-S-alkylenehydroxy,

when one Y is –NR^6-, and R^1 attached to it is –(CR^{12}R^{13})$_n$-C(O)-R^{14}, then the other YR^1 is selected from the group consisting of –NR^{15}R^{16}, -OR^7, and NR^6-(CR^{12}R^{13})$_n$-C(O)-R^{14};

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkylene-S-S-alkylene- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl;

Z is selected from the group of –CHR^{2}OH , -CHR^{2}OC(O)R^3, -CHR^{2}OC(S)R^3, -CHR^{2}OC(S)OR^3, -CHR^{2}OC(O)SR^3, -CHR^{2}OCO$_2$R^3, -OR^2 , -SR^2, -CHR^{2}N$_3$, -CH$_2$aryl, -CH(aryl)OH, -CH(CH=CR^2$_2$)OH, -CH(C≡CR^2)OH, -R^2 , -NR^2$_2$, -OCOR^3, -OCO$_2$R^3, -SCOR^3, -SCO$_2$R^3, -NHCOR^2, -NHCO$_2$R^3, -CH$_2$NHaryl, -(CH$_2$)$_p$-OR^{19}, and -(CH$_2$)$_p$-SR^{19}; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

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together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl and $-R^9$; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NH$aryl, $-CH_2$aryl; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkyleneoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D'' is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group consisting of O, N, and S;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, aryl, aralkyl, alkyloxycarbonyloxyalkyl, and lower acyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

R^7 is lower R^3;

each R^9 is independently selected from the group consisting of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group consisting of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group consisting of O, N, and S;

R^{18} is selected from the group consisting of –H and lower R^3;

R^{19} is selected from the group consisting of –H, and lower acyl;

R^{20} is selected from the group consisting of –H, lower R^3, and –C(O)-(lower R^3);

n is an integer from 1 to 3;

with the provisos that:

1) when X^3, X^4, or X^5 is N, then the respective J^3, J^4, or J^5 is null;

2) when G^2, G^3, or G^4 is O or S, then the respectiv J^2, J^3, or J^4 is null;

3) when G^3 or G^4 is N, then the respective J^3 or J^4 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

4) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

5) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$;

and pharmaceutically acceptable prodrugs and salts thereof.

Patent
45198.00042.RCE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Bookser *et al.*	
Serial No.: 09/801,933	Group Art Unit: 1624
Filed: March 7, 2001	Examiner: T. McKenzie
Title: **NOVEL ARYL FRUCTOSE-1,6-BISPHOSPHATASE INHIBITORS**	

Mail Stop RCE
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

INTERVIEW SUMMARY

On November 20, 2002, Examiner McKenzie conducted a telephonic interview with Applicants' attorneys Jessica Wolff and Diana Bush, Applicants' patent agent, Cynthia O'Donohue, and Dr. Mark Erion, with regard to Application Nos. 09/801,933, 09/518.501, and 09/747,182.

With regard to this Application, the following topics were discussed:

1. Examiner's indefiniteness rejection of "a fructose-1,6-bisphosphatase dependent disease" in claim 34 of the '933 application

The Examiner indicated that the Applicants can claim complications of diabetes. The Examiner also agreed that anything that inhibits glucose would be helpful in inhibiting the build-up of glycogen. The Examiner asked the Applicants to amend their claims to specifically name diabetes, complications of diabetes, and cardiovascular diseases.

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below.

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SAN/651522

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2. Examiner's indefiniteness and lack of enablement rejections for the term "prodrug" in claims 1-6 and 8-36 of the '933 application.

The Examiner indicated that he would give appropriate consideration to a declaration saying that a person of ordinary skill in the art could easily determine what is or is not a prodrug and that the preparation of prodrugs is routine. The Examiner also indicated that he would consider any publications showing the successful preparation and testing of prodrugs.

Respectfully Submitted,

Date: 5/27/03

By: Diana L. Bush

Diana L. Bush, Ph.D.
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JOC Article

Kinetics and Mechanism of the Aminolysis of Methyl 4-Nitrophenyl, Methyl 2,4-Dinitrophenyl, and Phenyl 2,4-Dinitrophenyl Carbonates

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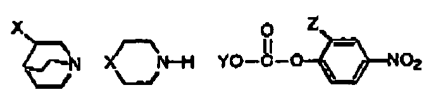
Received September 3, 2002

The reactions of methyl 4-nitrophenyl carbonate (MNPC) with a series of secondary alicyclic amines (SAA) and quinuclidines (QUIN), methyl 2,4-dinitrophenyl carbonate (MDNPC) with QUIN and 1-(2-hydroxyethyl)piperazinium ion (HPA), and phenyl 2,4-dinitrophenyl carbonate (PDNPC) with SAA are subjected to a kinetic investigation in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M. By following spectrophotometrically the nucleofuge release (330–400 nm) under amine excess, pseudo-first-order rate coefficients (k_{obsd}) are obtained. Plots of k_{obsd} vs [amine] at constant pH are linear, with the slope (k_N) being pH independent. The Brönsted-type plot (log k_N vs amine pK_a) for the reactions of SAA with MNPC is biphasic with slopes $\beta_1 = 0.3$ (high pK_a region) and $\beta_2 = 1.0$ (low pK_a region) and a curvature center at p$K_a^0 = 9.3$. This plot is consistent with a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$) and a change in the rate-determining step with SAA basicity. The Brönsted plot for the quinuclidinolysis of MNPC is linear with slope $\beta_N = 0.86$, in line with a stepwise process where breakdown of $T^{\pm}$ to products is rate limiting. A previous work on the reactions of SAA with MDNPC was revised by including the reaction of HPA. The Brönsted plots for the reactions of QUIN and SAA with MDNPC and SAA with PDNPC are linear with slopes $\beta = 0.51$, 0.48, and 0.39, respectively, consistent with concerted mechanisms. Since quinuclidines are better leaving groups from $T^{\pm}$ than isobasic SAA, yielding a less stable $T^{\pm}$, it seems doubtful that the quinuclidinolysis of PDNPC is stepwise, as reported.

Introduction

Although much attention has been drawn to the kinetics and mechanism of the aminolysis of aryl esters,[1] the aminolyses of alkyl aryl carbonates[2–4] and diaryl carbonates[5,6] have been less studied. The latter investigations include reports on the reactions of alkyl aryl carbonates with pyridines,[2] secondary alicyclic amines (SAA),[3] and benzylamines[4] and the reactions of diaryl carbonates with quinuclidines (QUIN)[5] and SAA.[6] Most of these reactions were found to proceed through a zwitterionic tetrahedral addition intermediate (stepwise mechanism),[2–5] and others were found to occur in a single step with no intermediate (concerted mechanism).[6] In all these studies, the Brönsted-type plot has been employed as an important tool for the diagnosis of the reaction mechanism.

To shed more light on the mechanisms of the aminolysis of carbonates, we describe in this work a kinetic study of the reactions of SAA and QUIN with methyl 4-nitrophenyl carbonate (MNPC), QUIN with methyl 2,4-dinitrophenyl carbonate (MDNPC), and SAA with phenyl 2,4-dinitrophenyl carbonate (PDNPC). We compare our results with those obtained for the same aminolysis of similar carbonates[3,5,6] to assess the effect of the nonleaving and leaving groups and the amine nature on the kinetics and mechanism of these reactions.



QUIN SAA MNPC (Y = Me, Z = H)
MDNPC (Y = Me, Z = NO_2)
PDNPC (Y = Ph, Z = NO_2)

In view of our kinetic results, in this work we also revise the kinetic data obtained for the reactions of SAA

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10.1021/jo026390k CCC: $22.00 © 2002 American Chemical Society
Published on Web 11/08/2002

TABLE 1. Experimental Conditions and k_{obsd} Values for the Aminolysis (SAA and QUIN) of Methyl 4-Nitrophenyl Carbonate (MNPC)[a]

amine	pH	F_N[b]	10^3 $[N]_{tot}$/M[c]	10^3 k_{obsd}/s^{-1}	no. of runs
piperidine	10.93	0.33	1.06–10.6	13.7–83.7	10
	11.24	0.50	1.06–10.6	28.0–118	9
	11.55	0.67	1.06–10.6	44.2–191	10
piperazine	9.63	0.33	2.51–25.1	4.80–54.5	9
	9.94	0.50	2.51–25.1	10.7–79.2	10
	10.25	0.67	2.51–25.1	13.7–112	10
1-(2-hydroxyethyl)-piperazine	9.07	0.33	0.49–4.94	3.90–26.4	10
	9.38	0.50	0.49–4.94	6.00–41.2	10
	9.69	0.67	0.49–4.94	12.3–58.2	10
morpholine	8.41	0.33	1.14–11.4	0.72–6.42	10
	8.78	0.50	1.14–11.4	1.64–9.33	9
	9.09	0.67	1.14–6.86	2.25–8.05	6
1-formylpiperazine	7.67	0.33	1.07–9.60	0.12–0.784	8
	7.98	0.50	1.07–10.7	0.20–1.38	9
	8.29	0.67	1.07–9.60	0.31–1.66	9
piperazinium ion	5.51	0.33	9.92–99.2	0.013–0.073	6
	5.81	0.50	11.9–83.0	0.019–0.126	5
	6.12	0.67	25.0–100.2	0.031–0.210	6
1-(2-hydroxyethyl)-piperazinium ion	4.60	0.0233	40.0–126	0.0055–0.0343	4
	4.90	0.0304	43.0–97.0	0.0154–0.0503	4
quinuclidine	8.5[d]	0.00126	0.80–8.0	0.67–2.78	7
	8.8[d]	0.00251	0.80–8.0	1.15–4.51	6
	9.0[d]	0.00397	0.80–8.0	2.20–7.26	7
3-hydroxy-quinuclidine	9.4	0.285	0.82–8.22	4.70–17.1	7
	9.7	0.443	0.82–8.22	4.30–20.9	6
	10.0	0.613	0.82–8.22	7.50–34.1	6
3-chloroqui-nuclidine	8.4	0.20	1.50–15.0	1.10–4.40	7
	8.7	0.33	1.50–15.0	1.70–7.70	7
	9.0	0.50	1.50–15.0	2.60–13.8	6
3-quinuclidinone	7.5	0.50	3.27–13.1	0.302–0.797	6
	7.8	0.67	1.31–13.1	0.361–1.04	7
	8.0	0.76	1.31–13.1	0.429–1.29	7

[a] In water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms). [d] In the presence of borate buffer 0.01M.

with MDNPC[2a] and discuss the mechanism proposed by Jencks for the reactions of quinuclidines with PDNPC.[5]

Experimental Section

Materials. The SAA were purified as described.[7] The substrates MNPC,[2a] MDNPC,[2b,8] and PDNPC[5] were synthesized as described previously. One of the products of the reactions of piperidine with MNPC and PDNPC, the methyl carbamate and phenyl carbamate of piperidine, respectively, were synthesized by the reactions of methyl and phenyl chloroformates with piperidine, as described.[9] Their NMR and IR spectra were in accordance with their structures.

Kinetic Measurements. These were carried out by means of a diode array spectrophotometer in aqueous solution, at 25.0 ± 0.1 °C, ionic strength 0.2 M (maintained with KCl). The reactions of MNPC, except those with piperazinium and 1-(2-(hydroxyethyl)piperazinium (HPA) ions, were followed at 400 nm (appearance of the 4-nitrophenoxide anion). The reactions of MNPC with the above ions, carried out at low pH, were followed at 330 nm (appearance of 4-nitrophenol). The quinuclidinolysis of MDNPC and the reactions of this substrate with HPA, as well as the reactions of PDNPC with all the SAA were studied at 360 nm (following the appearance of 2,4-dinitrophenoxide anion).

All reactions were investigated under an excess of the amine over the substrate (13-fold at least). The initial substrate concentration was 2.5×10^{-5} M.

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TABLE 2. Experimental Conditions and k_{obsd} Values for the Aminolysis (QUIN and HPA) of Methyl 2,4-Dinitrophenyl Carbonate (MDNPC)[a]

amine	pH	F_N[b]	10^3 $[N]_{tot}$/M[c]	10^3 k_{obsd}/s^{-1}	no. of runs
quinuclidine	8.5[d]	0.00126	0.42–4.2	29.6–139	7
	8.8[d]	0.00251	0.42–4.2	61.0–326	6
	9.0[d]	0.00397	0.42–4.2	106–539	7
3-hydroxy-quinuclidine	9.4	0.285	0.49–4.89	14.3–138	6
	9.7	0.443	0.49–4.19	17.7–195	6
	10.0	0.613	0.49–4.89	26.7–245	7
3-chloro-quinuclidine	8.4	0.20	1.53–15.3	17.0–126	7
	8.7	0.33	1.53–15.3	23.0–221	6
	9.0	0.50	1.53–15.3	32.0–312	7
3-quinuclidinone	7.5	0.50	0.95–9.54	1.50–13.8	7
	7.8	0.67	0.95–9.54	3.20–22.2	6
	8.0	0.76	0.95–9.54	2.30–20.0	6
1-(2-hydroxyethyl)-piperazinium ion (HPA)	4.16	0.0128	10–40	0.07–0.35	3
	4.36	0.0174	10–45	0.11–0.71	3
	4.60	0.0233	10–100	0.21–2.2	6

[a] In water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms). [d] In the presence of borate buffer 0.01M.

Pseudo-first-order rate coefficients (k_{obsd}) were found for all the reactions; these were determined by means of the spectrophotometer kinetic software for first-order reactions.

Three pH values were employed in the reactions with each amine. These pH values were maintained by the amine as its own buffer (pH near the pK_a of its conjugate acid), except in the reactions of MNPC and MDNPC with quinuclidine and that of PDNPC with piperidine, where external buffer was used. For the reactions of the three substrates with HPA, the pH was maintained by partial ionization of 1-(2-hydroxyethyl)-piperazinium dication, whose pK_a is 4.56 under the kinetic conditions.[10] Under these conditions, the pK_a value of the conjugate acid of HPA is 5.9.[10]

The k_{obsd} values and the experimental conditions for the reactions of MNPC with SAA and QUIN are shown in Table 1. Those for the reactions of MDNPC with QUIN and HPA are exhibited in Table 2, and those for the reactions of PDNPC with SAA can be seen in Table 3.

Product Studies. 4-Nitrophenoxide anion and 2,4-dinitrophenoxide anion were identified as one of the products of the aminolysis of MNPC and PDNPC, respectively. This was achieved by comparison of the UV–vis spectra after completion of these reactions with those of authentic samples of sodium 4-nitrophenoxide or sodium 2,4-dinitrophenoxide, under the experimental kinetic conditions. The other product of the reactions of MNPC and PDNPC with piperidine was identified as the methyl carbamate of piperidine and the phenyl carbamate of piperidine, respectively. The identification was carried out by HPLC through a comparison of the retention times of authentic samples with those after completion of the reactions. HPLC conditions: column, Supelcosil LC-18-DB (25 cm, 5 μm); eluant, acetonitrile/water = 50/50; isocratic mode, 0.4 mL/min.

Results and Discussion

The kinetic law obtained under the reaction conditions is that described in eq 1,

$$\frac{d[P]}{dt} = k_{obsd}[S] \qquad (1)$$

where P is 4-nitrophenoxide anion (4-nitrophenol in the reaction of MNPC with piperazinium ion and HPA) or 2,4-dinitrophenoxide anion, S is the substrate, and k_{obsd}

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TABLE 3. Experimental Conditions and k_{obsd} Values for the Aminolysis (SAA) of Phenyl 2,4-Dinitrophenyl Carbonate (PDNPC)[a]

amine	pH	F_N[b]	10^3 [N]$_{tot}$/M[c]	10^3 k_{obsd}/s^{-1}	no. of runs
piperidine	7.70[d]	0.00029	4.27−21.3	0.383−0.593	5
	8.00[d]	0.00058	4.27−21.3	0.563−1.22	12
	8.30[d]	0.00115	4.27−21.3	1.32−1.94	8
piperazine	9.64	0.339	4.21−25.3	55.8−27.5	6
	9.94	0.500	4.21−25.3	101−367	6
	10.24	0.667	4.07−24.4	111−260	6
1-(2-hydroxyethyl)-piperazine	9.08	0.333	6.85−41.1	26.4−139	11
	9.38	0.500	5.80−34.8	42.8−161	6
	9.68	0.667	5.30−26.5	33.8−154	6
morpholine	8.48	0.333	4.02−24.1	15.8−86.5	11
	8.78	0.500	4.02−24.1	17.6−113	11
	9.08	0.667	4.02−24.1	43.0−151	6
1-formylpiperazine	7.68	0.333	3.23−11.3	11.8−39.9	5
	7.98	0.500	4.68−29.1	14.4−44.0	5
	8.28	0.667	3.24−22.6	20.0−68.9	7
piperazinium ion	5.51	0.333	4.03−24.2	1.09−3.78	6
	5.81	0.500	4.18−25.1	1.29−5.70	6
	6.11	0.667	4.32−26.0	1.21−1.08	10
1-(2-hydroxyethyl)-piperazinium ion	4.60	0.0233	4.38−30.7	0.365−0.681	7
	4.80	0.0282	4.58−27.5	0.42−0.756	6

[a] In water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms). [d] In the presence of borate buffer 0.01M.

TABLE 4. Values of pK_a for the Conjugate Acids of Secondary Alicyclic Amines (SAA) and k_N Values for the Reactions of SAA with Methyl 4-Nitrophenyl Carbonate (MNPC), Methyl 2,4-Dinitrophenyl Carbonate (MDNPC) and Phenyl 2,4-Dinitrophenyl Carbonate (PDNPC)[a]

		k_N/s^{-1} M^{-1}		
amine	pK_a	MNPC	MDNPC[b]	PDNPC
piperidine	11.24	26 ± 1	280 ± 17	520 ± 24
piperazine	9.94	6.4 ± 0.1	166 ± 17	318 ± 12
1-(2-hydroxyethyl) piperazine	9.38	1.7 ± 0.1	73 ± 10	85 ± 3
morpholine	8.78	1.6 ± 0.1	41 ± 4	83 ± 3
1-formylpiperazine	7.98	0.26 ± 0.01	9 ± 1	31 ± 2
piperazinium ion	5.81	0.031 ± 0.002	1.4 ± 0.1	5.4 ± 0.4
1-(2-hydroxyethyl)-piperazinium ion	5.9	0.067 ± 0.005	1.1 ± 0.1[c]	5.0 ± 0.2

[a] Both the pK_a and k_N values were determined in aqueous solution, at 25.0 °C, and an ionic strength of 0.2 M (KCl). [b] Data from ref 3a, except otherwise stated. [c] Datum obtained in this work.

is the pseudo-first-order rate coefficient (excess of amine was used throughout).

Plots of k_{obsd} against [amine] at constant pH were linear, in accordance with eq 2,

$$k_{obsd} = k_0 + k_N[\text{amine}] \tag{2}$$

where k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrates, respectively. In general, k_0 and k_N were pH independant, except in the reaction of MNPC with piperidine, where k_0 was dependent on pH. The values of k_0 for the hydrolysis of MNPC are 10^2k_0/s^{-1} = 0.5, 1.5, and 2.4 at pH = 10.93, 11.24, and 11.55, respectively.

The values of k_N (obtained as the slopes of plots of eq 2) for the reactions of SAA with MNPC, MDNPC, and PDNPC are shown in Table 4. The data for MDNPC, mostly taken from a previous study,[3a] include the datum for HPA (this work). These values, as well as those of

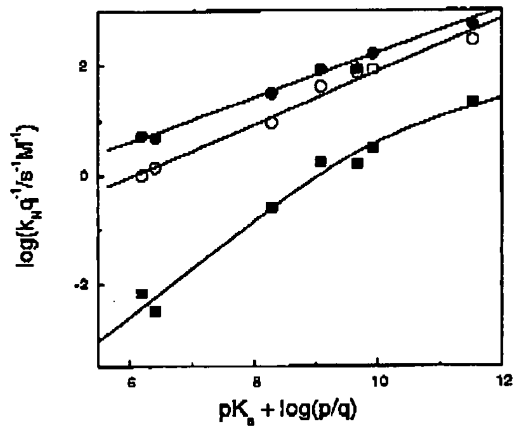


FIGURE 1. Brønsted-type plots for the reactions of SAA with MNPC (■), MDNPC (○), and PDNPC (●) in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M (KCl).

TABLE 5. Values of pK_a for the Conjugate Acids of Quinuclidines (QUIN) and k_N Values for the Reactions of QUIN with Methyl 4-Nitrophenyl Carbonate (MNPC) and Methyl 2,4-Dinitrophenyl Carbonate (MDNPC)[a]

		k_N/s^{-1} M^{-1}	
amine	pK_a	MNPC	MDNPC
quinuclidine	11.4	20 ± 1	305 ± 11
3-hydroxyquinuclidine	9.8	0.58 ± 0.03	81 ± 5
3-chloroquinuclidine	9.0	0.17 ± 0.01	41 ± 1
3-quinuclidinone	7.5	0.009 ± 0.0004	3.0 ± 0.2

[a] Both the pK_a and k_N values were determined in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M (KCl).

the pK_a of the conjugate acids of the amines, were statistically corrected with $q = 2$ for piperazine and $p = 2$ for all the conjugate acids of the amines, except that for piperazinium ion with $p = 4$.[10,11] With these corrected values the Brönsted-type plots (shown in Figure 1) were obtained.

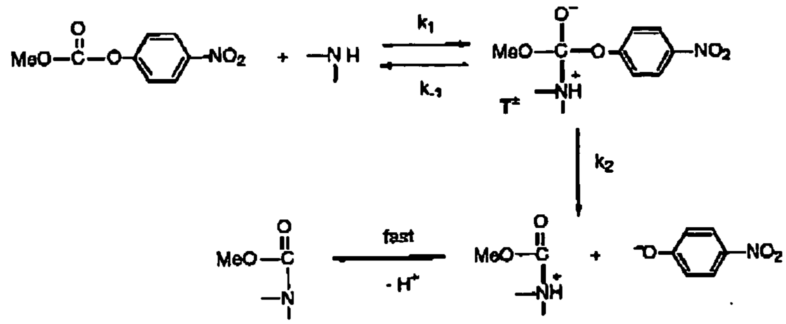
The k_N values found for the quinuclidinolysis of MNPC and MDNPC are shown in Table 5; the corresponding Brönsted plots are exhibited in Figure 2.

The nonlinear Brönsted plot for the reactions of SAA with MNPC (Figure 1) can be explained by the mechanism described in Scheme 1, where NH represents a SAA. The Brönsted break results from a change in the rate-determining step, from breakdown of the zwitterionic tetrahedral intermediate ($T^{\pm}$) to products (k_2 step) to $T^{\pm}$ formation (k_1 step) as the amine basicity increases.[2,3a,5−7,10]

The curved line for MNPC in Figure 1 was calculated by means of a semiempirical equation based on the existence of the intermediate $T^{\pm}$ in Scheme 1.[2,5−7,10] This equation contains four parameters: β_1 and β_2, which are the Brönsted slopes at high and low pK_a, respectively, and $k_N{}^0$ and $pK_a{}^0$, which are the corresponding values at the center of the curvature. The Brönsted curve for MNPC was calculated with the following parameters: log $k_N{}^0 = 0.232$, $pK_a{}^0 = 9.3$, $\beta_1 = 0.3$ and $\beta_2 = 1.0$ ($n = 7$, $R = 0.994$). The errors of the slopes are ±0.1, and those of $pK_a{}^0$ and log $k_N{}^0$ are ±0.2 and ±0.1, respectively.

(11) Bell, R. P. *The Proton in Chemistry*, Methuen: London, 1959; p 159.

SCHEME 1



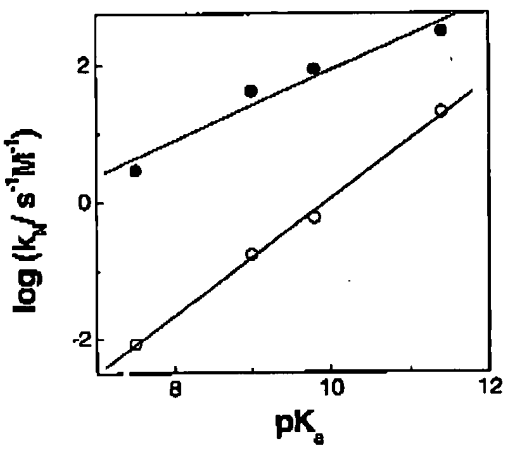


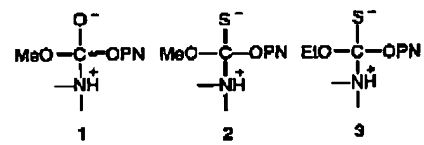
FIGURE 2. Bronsted-type plots for the quinuclidinolysis of MNPC (O) and MDNPC (●) in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M (KCl).

The values of β_1 and β_2 for the aminolysis of MNPC are in accord with those reported for other reactions governed by stepwise mechanisms: $\beta_1 = 0.1-0.3$ and $\beta_2 = 0.8-1.1$.[2,5-7,10]

The simple mechanism shown by the reactions of SAA with MNPC (Scheme 1) is in contrast with the more complex one exhibited by the reactions of the same amines with methyl 4-nitrophenyl thionocarbonate (MNPTOC)[12] and ethyl 4-nitrophenyl thionocarbonate (ENPTOC).[13] In these cases there is an additional path for the intermediate $T^{\pm}$ in Scheme 1: its deprotonation by the corresponding amine to yield an anionic tetrahedral intermediate (k_3 step). On the basis of the nonlinear upward k_{obsd} vs [SAA] plots obtained in these reactions, it was concluded that the rate constant for proton transfer (k_3[SAA]) is similar to that for the nucleofuge expulsion from $T^{\pm}$ (k_2).[12,13] Since the value of k_3 and the concentration range of SAA are similar for the reactions of MNPC and the thiono derivatives (see below), it follows that the simpler reaction scheme for the carbonate arises from its larger k_2 value compared to that for the thionocarbonates MNPTOC and ENPTOC.

(12) Castro, E. A.; Saavedra, C.; Santos, J. C.; Umaña, M. I. *J. Org. Chem.* **1999**, *64*, 5401.
(13) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501.

The k_3 values for MNPC and the thiono derivatives should be similar, since the proton transfers from the intermediates **1**, **2**, and **3** (PN = 4-nitrophenyl) to the



corresponding free amine are thermodynamically favorable.[12,13] Therefore, these processes are diffusion-controlled and a value of 10^{10} s^{-1} M^{-1} has been estimated for k_3.[12-14]

The faster 4-nitrophenoxide expulsion (larger k_2 value) from intermediate **1** relative to that from **2** or **3** is reasonable in view of the greater ability of O^- in **1** compared to S^- in **2** or **3** to form a double bond with C and expel the nucleofuge. This has been ascribed to the stronger π-bonding energy of the carbonyl group than that of thiocarbonyl.[15]

The quinuclidinolysis of MNPC shows a linear Brönsted plot (Figure 2) of slope $\beta = 0.86 \pm 0.05$. This slope value is consistent with a pathway through a zwitterionic tetrahedral intermediate ($T^{\pm}$) whose breakdown to products is rate determining. Namely, these reactions behave according to Scheme 1, with the formation of $T^{\pm}$ as an equilibrium step and the k_2 step as rate limiting ($k_{-1} \gg k_2$ in Scheme 1).

The linear Brönsted plot for the reactions of MNPC with QUIN, in contrast to the biphasic plot for the reactions of this substrate with SAA, can be attributed to the fact that QUIN are better nucleofuges from a tetrahedral intermediate than isobasic SAA.[16] The pK_a value at the Brönsted curvature center (pK_a^0) is related to the k_{-1}/k_2 ratio, as described in eq 3,[17]

$$\log(k_{-1}/k_2) = (\beta_2 - \beta_1)\,(\mathrm{p}K_a^{\,0} - \mathrm{p}K_a) \qquad (3)$$

where β_1 and β_2 are the Brönsted slopes for formation and breakdown of the intermediate $T^{\pm}$, respectively.

(14) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.
(15) Hill, S. V.; Thea, S.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 437. Cottrell, T. L. *The Strengths of Chemical Bonds*, 2nd ed; Butterworth: London, 1959; p 275. Kwon, D. S.; Park, H. S.; Um, I. H. *Bull. Korean Chem. Soc.* **1991**, *12*, 93.
(16) Castro, E. A.; Muñoz, P.; Santos, J. C. *J. Org. Chem.* **1999**, *64*, 8298.
(17) Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126.

Since β_1 and β_2 are little dependent on the amine nature[1b,c,2,5,7,10] and pK_a^0 is larger for the QUIN reactions (its pK_a^0 value is larger than 11.4, according to Figure 2), it follows from eq 3 that the k_{-1}/k_2 ratio is larger for a given QUIN compared to an isobasic SAA. Since the k_2 value should be independent of the amine nature and basicity,[5] it follows that the value of k_{-1} is larger for a QUIN than for an isobasic SAA. Therefore, the lack of Brönsted curvature within the pK_a range 7.5–11.4 for the reactions of MNPC with QUIN can be explained by a larger nucleofugality from T$^{\pm}$ of QUIN compared to an isobasic SAA. A similar result was found in the reactions of QUIN and SAA with ethyl S-(4-nitrophenyl) thiolcarbonate.[16]

The Brönsted plots (statistically corrected) for the reactions of MDNPC and PDNPC with SAA are shown in Figure 1. The Brönsted plot for the quinuclidinolysis of the former substrate is exhibited in Figure 2. The three plots are linear with slope (β) values of 0.48 ± 0.05, 0.39 ± 0.05, and 0.51 ± 0.08, respectively.[18] The magnitude of these β values suggests that these reactions are concerted. Similar β values have been found in the concerted aminolysis of related substrates. Linear Brönsted plots with slopes $\beta = 0.56$ and 0.48 are exhibited in the reactions of SAA with *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) ethyl thiolcarbonates.[19] In the reactions of the same amines with methyl 2,4,6-trinitrophenyl carbonate, a β value of 0.36 was found.[2b] Also, the concerted methoxycarbonyl transfer from *N*-(methoxycarbonyl)isoquinolinium to pyridines shows a linear Brönsted plot of slope $\beta = 0.58$.[20]

The value of the Brönsted β alone is not sufficient for the diagnosis of a concerted mechanism.[21] It is also important to calculate the hypothetical pK_a^0 value (pK_a at the center of the Brönsted curvature) for a stepwise mechanism; the lack of Brönsted curvature within the pK_a range of the nucleophiles employed is a clear indication of a concerted mechanism.[21]

A biphasic Brönsted plot was found in the stepwise pyridinolysis of MDNPC in water, with pK_a^0 = 7.8.[2b] It is known that SAA are better nucleofuges from a tetrahedral intermediate than isobasic pyridines, as judged by the larger pK_a^0 values found for the former amines. For instance, the pK_a^0 values for the reactions of 2,4-dinitrophenyl acetate with pyridines and SAA are 7.3 and 9.1, respectively.[2c,22] Similarly, for the reactions of 2,4-dinitrophenyl thiolacetate with pyridines and SAA, the pK_a^0 values obtained are 6.6 and 8.9, respectively.[10] Namely, there is a pK_a^0 increase of ca. 2 units in going from pyridines to SAA. Assuming a similar increase for the reactions of carbonates, a pK_a^0 value of 9.8 (7.8 + 2) can be estimated for the hypothetical stepwise reactions of SAA with MDNPC. Nevertheless, this pK_a^0 value cannot be larger than that for the same aminolysis of MNPC (9.3, this work), since 2,4-dinitrophenoxide is a better leaving group than 4-nitrophenoxide.[1b,c,5] Therefore, it seems that the pK_a^0 increase (from pyridines to SAA) of ca. 2 pK_a units for acetates cannot be applied to carbonates. We can only assume that the pK_a^0 value for the hypothetical stepwise reactions of SAA with MDNPC should be larger than 7.8 but smaller than 9.3.

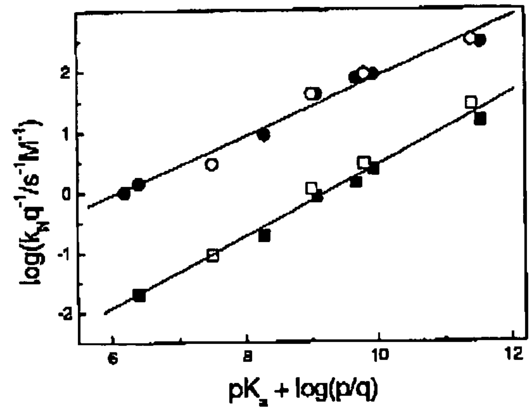


FIGURE 3. Bronsted-type plots for the reactions of MDNPC (this work) with QUIN (○) and SAA (●) and those of EDNPTC with QUIN (□, ref 16) and SAA (■, ref 19a) in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M (KCl).

As seen in Figure 1, there is no break within this pK_a range in the corresponding Brönsted plot. Therefore, we conclude that the reactions of SAA with MDNPC are concerted. Since QUIN are better leaving groups from a tetrahedral intermediate than isobasic SAA (see above), it follows that the reactions of QUIN with MDNPC should also be concerted, in view of the greater instability of the hypothetical intermediate formed with QUIN than that with SAA.

Another proof for concertedness of the above reactions is the similar reactivity pattern of QUIN and SAA toward MDNPC and its thiol derivative ethyl S-(2,4-dinitrophenyl) thiolcarbonate (EDNPTC, see Figure 3).[23,24] It is known that the latter reactions are concerted.[16,19a] As seen in this figure, these two amine series are equally reactive toward a given substrate, and the Brönsted slope values for the aminolysis of these substrates are very similar.

The fact that the reactions of SAA with MNPC are stepwise, whereas those of these amines with MDNPC are concerted, means that the tetrahedral intermediate T$^{\pm}$ is greatly destabilized by the introduction of a second nitro group in the nucleofuge. This should be due to the much greater nucleofugality of 2,4-dinitrophenoxide from the hypothetical dinitro intermediate compared to that of 4-nitrophenoxide from 1, which destabilizes it kinetically. A similar situation was found in the reactions of

(18) The Brönsted-type plot for the reactions of SAA with MDNPC appeared as nonlinear in our original work (ref 3a) and the stepwise mechanism was preferred to the concerted one. The reason for the curved plot was that the point for the piperazinium ion was wrongly located in the plot, although the k_N value in the table was correct. In this work we checked this k_N value and obtained a similar one. With this point rightly located, the Brönsted plot becomes linear. To be sure of the linearity, we also measured (in this work) the k_N value for the reaction of this substrate with 1-(2-hydroxyethyl)piperazinium ion (see Table 2). As seen in Figure 1, with these two new points, the Brönsted plot for MDNPC looks linear.

(19) (a) Castro, E. A.; Ibañez, F.; Salas, M.; Santos, J. G. *J. Org. Chem.* 1991, *56*, 4819. (b) Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* 1994, *59*, 30.

(20) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* 1987, *109*, 3040.

(21) Williams, A. *Acc. Chem. Res.* 1989, *22*, 387.

(22) Castro, E. A.; Ureta, C. *J. Org. Chem.* 1990, *55*, 1676.

(23) The change of methoxy to ethoxy as the nonleaving group of carbonates has very little effect on the rate constants involved in these reactions.[24]

(24) Castro, E. A.; Cubillos, M.; Santos, J. G.; Tellez, J. *J. Org. Chem.* 1997, *62*, 2512.

SAA with the corresponding thiol derivatives: The reactions of ethyl S-4-nitrophenyl thiolcarbonate are stepwise,[25] in contrast to those of EDNPTC, which are concerted.[19a]

The reactions of SAA with 4-methylphenyl 4-nitrophenyl carbonate in aqueous ethanol have been found to be stepwise.[6] It is known that a zwitterionic tetrahedral intermediate ($T^{\pm}$) is more stabilized in the more polar solvents.[5] Therefore, these reactions should also be stepwise in water. On the other hand, the change of Me to H in the nonleaving group of the substrate should not change the mechanism, as indicated by the similar inductive effects[26,27] of 4-MePhO and PhO.[6] Therefore, it is very likely that the reactions of SAA with PNPC in water are stepwise.

Another indication that the above reactions are stepwise is the fact that the quinuclidinolysis of PNPC is stepwise, as evidenced by the linear Brönsted plot of slope 1.0 obtained.[5] If these reactions are stepwise, it is more likely that the reactions of this substrate with SAA are stepwise in view of the slower nucleofugality of SAA from the intermediate $T^{\pm}$ than isobasic QUIN (see above), which stabilizes this intermediate.[16]

The fact that the reactions of SAA with PDNPC in water are concerted, whereas those of the same amines with PNPC in the same solvent are stepwise, is another example of the great destabilization caused to the $T^{\pm}$ species by the addition of a second nitro group to the nucleofuge of the substrate.

The greater reactivity of PDNPC than MDNPC toward SAA (Table 4 and Figure 1) is in contrast to the larger rate constant for SAA attack, to form the zwitterionic tetrahedral intermediate (k_1), on methyl 4-nitrophenyl thionocarbonate compared to that on phenyl 4-nitrophenyl thionocarbonate.[12] The latter result was attributed to the greater steric hindrance of phenyl relative to methyl toward SAA attack, despite the greater electron-withdrawing effect of PhO compared to MeO in the corresponding thionocarbonates.[12] These contradicting results could be explained by assuming that steric hindrance is less important for a concerted mechanism than a stepwise process through the tetrahedral species.

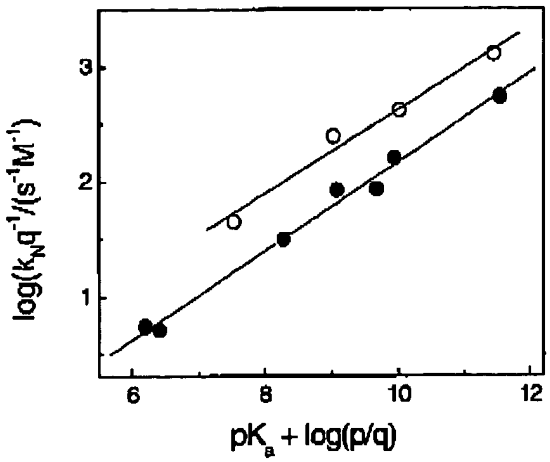


FIGURE 4. Bronsted-type plots for the reactions of PDNPC with QUIN (O) and SAA (●) in aqueous solution, at 25.0 °C and an ionic strength of 0.2 M (KCl). The data for QUIN was replotted from ref 5.

The quinuclidinolysis of PDNPC in water has been described as stepwise, through a zwitterionic tetrahedral intermediate.[5] On the other hand, quinuclidines are known to be better nucleofuges from a zwitterionic intermediate than isobasic SAA (see above).[16] This means that quinuclidines destabilize the tetrahedral intermediate relative to isobasic SAA.[16] Since we have found in this work that the reactions of SAA with PDNPC are concerted, it is doubtful that the reactions of quinuclidines with the same substrate be stepwise. Careful examination of the Brönsted-type plot obtained for the latter reactions shows that the points are better accommodated by a linear relation rather than a biphasic one (see Figure 4). The linear plot shows a slope $\beta = 0.36 \pm 0.05$ ($R^2 = 0.98$), which is very similar to that found by us in the reactions of SAA with the same substrate (Figure 4, $\beta = 0.39 \pm 0.05$).

Acknowledgment. We thank FONDECYT of Chile (project 1020538) for financial assistance.

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(25) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* 1994, *59*, 3572.
(26) The inductive effects exerted by a substituent in a tetrahedral species are more important than the resonance effects.[27]
(27) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* 1973, *95*, 5637. Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* 1974, *96*, 1436.